CARDIOVASCULAR MEDICINE

Economic evaluation of the impact of nicorandil in angina (IONA) trial

A Walker, J McMurray, S Stewart, W Berger, A D McMahon, H Dargie, K Fox, S Hillis, N J K Henderson, I Ford

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See end of article for authors' affiliations

Correspondence to: Dr A Walker, Robertson Centre for Biostatistics, Boyd Orr Building, University of Glasgow, Glasgow G12 8QQ, UK; andreww@stats.gla.ac.uk

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Objective: To estimate the net cost of adding nicorandil to usual treatment for patients with angina and to compare this with indicators of health benefit.
Design: Cost effectiveness analysis
Setting: Based on results of the IONA (impact of nicorandil on angina) trial.
Patients: Patients with angina fulfilling the entry criteria for the IONA trial
Interventions: In one arm of the trial nicorandil was added to existing antianginal treatment and compared with existing treatment alone.
Main outcome measures: Costs were for use of hospital resources (for cardiovascular, cerebrovascular, and gastrointestinal reasons), nicorandil, and care after hospital discharge. Benefits were assessed in three ways: (1) IONA trial primary outcome (coronary heart disease (CHD) death, non-fatal myocardial infarction, or hospital admission for cardiac chest pain); (2) acute coronary syndrome (CHD death, non-fatal myocardial infarction, or unstable angina); and (3) event-free survivors at the end of the trial.
Results: The net cost for each additional IONA trial end point averted was −£5 (−€7). The net cost for each case of acute coronary syndrome averted was −£8 (−€12). The net cost for each event-free survivor was −£5 (−€7). These figures are based on gastrointestinal events that were judged definitely or probably related to nicorandil. When all gastrointestinal events were included these three ratios rose to £567 (€835), £886 (€1305), and £516 (€760), respectively.
Conclusions: A substantial amount of the additional cost of nicorandil is offset by reduced use of hospital services. The limited comparisons possible with other CHD interventions suggest that nicorandil compares favourably.

Angina pectoris is one of the most common cardiovascular conditions treated by physicians.[1–3] In addition to having symptomatic limitation, patients with angina require long term drug treatment, are often admitted to hospital (with an exacerbation of angina or an acute coronary syndrome), and often require revascularisation (percutaneous coronary intervention or coronary artery bypass grafting).[4–6] As a result of these factors, the treatment of angina pectoris consumes a substantial proportion of overall spending on health care, most of which relates to hospital admissions and revascularisation.[7–9] This burden is rising relentlessly because of the increasing numbers of both elderly people (who are at most risk of coronary heart disease (CHD)) and long term survivors with CHD in the aging populations.[10–12]

The largest parts of the direct health care costs of angina are those due to hospital admissions and revascularisation procedures or operations.[4–8] Consequently, new treatments for angina that can reduce admission and revascularisation rates have a good prospect of being cost effective. This must, however, be proved rather than simply assumed.

Nicorandil is an antianginal drug that opens ATP sensitive potassium channels and acts as a nitrate.[13] As well as anti-ischaemic effects, nicorandil may have a cardioprotective action.[13] The IONA (impact of nicorandil in angina) trial was carried out in the UK in which 5126 high risk angina patients were randomly assigned to receive either placebo (n = 2561) or nicorandil 20 mg (n = 2565) twice daily in addition to full conventional treatment.[14 15] As already reported, nicorandil reduced the risk of the primary composite end point (CHD death, non-fatal myocardial infarction (MI), or unplanned hospitalisation with cardiac chest pain) by 17% (p = 0.014) over a mean follow up of 1.6 years.[15] Data on revascularisations and other resource utilisation were also collected. This report describes an economic evaluation of the IONA trial.

METHODS

The intention to treat analysis of the IONA trial was used to estimate costs and benefits over the duration of the trial (no longer term projection was made). This analysis was carried out from the perspective of the NHS. Only direct costs were considered, and future costs and benefits were not discounted to their present value because of the limited duration of follow up.

Treatment options compared

The treatment options compared in the trial were also used in the economic evaluation—in other words, standard background antianginal treatment alone compared with the same treatment options with the addition of nicorandil. Background antianginal treatment was not specified in the trial protocol, which allowed the investigator to judge the optimal treatment for the individual patient.[14] In IONA 57% of patients were treated with a β blocker, 55% with a calcium channel blocker, and 87% with a nitrate; 88% were taking aspirin. ''Standard background antianginal treatment'' is, hereafter, referred to as ''usual care''.

Abbreviations: CCU, coronary care unit; CHD, coronary heart disease; ICU, intensive care unit; IONA, impact of nicorandil on angina; MI, myocardial infarction; NICE, National Institute for Health and Clinical Excellence

Costs and offsets included

Only net incremental costs and benefits were calculated: costs that were similar in both treatment arms of the trial were not considered (for example, background pharmacological treatment). The additional costs quantified were the cost of nicorandil (including dispensing costs and the cost of additional physician visits) and the cost of adverse events related to nicorandil. The cost offsets considered were reductions in hospital admissions, including care when a patient is admitted for procedures or surgical operations. The net cost was compared with the net gain, in terms of the primary outcome measure (as well as numbers of acute coronary syndromes and number of event-free survivors), to describe the cost effectiveness of nicorandil in the IONA trial.

Costs used in the analysis

Cost of nicorandil and associated costs

In IONA, all patients randomly assigned to the nicorandil group received an initial eight week prescription for 10 mg twice daily for two weeks followed by 20 mg twice daily thereafter. All patients were assumed to have received this treatment. Subsequently, patients were re-evaluated at four monthly intervals and a repeat prescription was issued at each visit. The dose prescribed at each visit was the one used in this analysis. A 10 mg tablet costs 13.6 pence and a 20 mg tablet, 25.9 pence.[16] A 10% dispensing fee was added for each prescription. The cost of two general practitioner visits (£19 a visit) was added to allow for the initiation and uptitration of nicorandil.[17]

Hospital admissions, procedures, and surgical operations

Data on all hospitalisations and procedures were collected prospectively during the trial. Investigators completed a form describing the primary diagnosis or main procedure, date of admission, and date of discharge (including day case procedures). The number of days during the admission spent on a coronary (CCU) or intensive care unit (ICU) was also recorded.

The daily costs applied were £429 (€632) for a specialist cardiology ward, £666 (€981) for a cardiac surgery ward, £242 (€357) for a general medical ward, £1323 (€1949) for ICU, and £610 (€899) for CCU.[17 18] As the information collected in the trial did not distinguish between ICU and CCU, the daily costs of these two types of bed were averaged (£967 (€1 425)). For day case procedures, figures of £365 (€538) and £622 (€916) were used for general medicine and cardiothoracic surgery, respectively.[18] These costs are for the year ending 31 March 2002.

In addition, we allowed for follow up consisting of two hospital outpatient visits (£72 (€106) each)[17] and two general practitioner visits (£19 (€28) each) for each hospital episode.[18] This was included in a secondary analysis (see below under ''Cost of potential adverse effects'').

Only cardiovascular and cerebrovascular events were considered in this analysis. Procedures and surgical operations were not costed separately—that is, only bed day costs were used. Post-discharge outpatient follow up was not included in the primary analysis of costs but they were included in a secondary analysis reported in the results below.

Data on length of stay were not available for 18 of the 5126 randomly allocated patients (seven in the nicorandil arm and 11 in the placebo arm) and they were omitted from the analysis below.

Cost of potential adverse effects

The use of nicorandil was associated with a significant excess of gastrointestinal admissions in IONA. These were evaluated in two separate ways. In the primary analysis, only those admissions thought by the investigator to be treatment related were costed. In the secondary analysis all admissions were costed and in addition all outpatient costs were included. In both analyses, the hospital bed day costs used were those for a general medical ward.

Analyses carried out

The primary analysis assessed the costs of nicorandil, the extra costs related to definite gastrointestinal adverse events, and the reduction in costs related to fewer hospital admissions. The secondary analysis assessed the costs of nicorandil, all gastrointestinal adverse events, hospital cost reductions, and the costs of post-discharge care.

Incremental cost effectiveness ratios were calculated. These compare the total cost and benefit in each of the two arms and are expressed as the difference in costs divided by the difference in benefits. Three different incremental cost effectiveness ratios were calculated. The numerator (difference in total costs between the two groups) was identical in each case. The denominator (difference in benefits between the two groups) varied as follows: (1) the primary end point of the IONA clinical trial (CHD death, non-fatal MI, or hospital admission for cardiac chest pain); (2) cases of definite acute coronary syndromes observed in the trial (CHD death, non-fatal MI, or unstable angina); and (3) the number of people free from any major cardiovascular event (defined as CHD death, non-fatal MI, unstable angina, definite or probable angina, and stroke or hospital admission for transient ischaemic attack) at the end of the trial.

Sensitivity analysis

The sensitivity analysis focused on likely changes in clinical practice and uncertainties in our assumptions about the setting for treating patients. Firstly, in the UK, National Institute for Health and Clinical Excellence (NICE) guidance on the role of stents in angioplasty was predicted to increase usage from around 69% to between 75 and 80%.[19] In addition, NICE is evaluating the role of drug eluting stents; if recommended these will also increase the cost of each procedure (while possibly reducing the restenosis rate). We thus increased the cost of angioplasty by £100, £200, and £500 to allow for increases in cost per procedure. Secondly, we raised and lowered the cost of a bed day by 20% for cardiology, cardiac surgery, and ICU/CCU.

Table 1 Gastrointestinal adverse events and hospitalisations

	Usual care (n = 2561)	Usual care plus nicorandil (n = 2565)
Only patients whose event was certainly, probably, or possibly due to the trial drug		
Patients	18	35
Admissions	16	31
Bed days, general medical ward	60	183
Bed days, ICU	1	0
Net extra bed days	+123 on general ward, −1 on ICU	
Net extra cost	£28443	
All patients with a gastrointestinal event		
Patients	132	194
Admissions	124	185
Bed days, general medical ward	557	924
Bed days, ICU	14	10
Net extra bed days	+367 on general ward, −4 on ICU	
Net extra cost	£83522	

ICU, intensive care unit.

Table 2 Numbers of hospital admissions and patients hospitalised in the IONA (impact of nicorandil on angina) trial with a cardiovascular or cerebrovascular diagnosis

	Usual care	Usual care plus nicorandil	Nicorandil impact
Number of patients randomly allocated	2561	2565	
All patients			
Hospital admissions	1132	968	−164
Days in hospital	6154	5230	−924
Days in hospital/admission*	5.4 (11)	5.4 (11.1)	0
Hospital admissions/patient	0.44	0.38	−0.06
Days in hospital/patient*	2.4 (8)	2.0 (9)	−0.4
Patients hospitalised			
Patients hospitalised	683	609	−74
Admissions/patient hospitalised	1.66	1.59	−0.07
Days in hospital/patient hospitalised	9.0	8.6	−0.4

*Mean (SD).

RESULTS

Cost of nicorandil

A starter pack consisting of 28 times 10 mg tablets and 84 times 20 mg tablets was given to 2565 patients. Subsequently 492 packs of 10 mg tablets and 7971 packs of 20 mg tablets (each pack containing 182 tablets) were dispensed.

The total cost of nicorandil was £453 487 (€680 082). This rose to £498 834 (€734 887) with the 10% dispensing fee and to £596 304 (€894 481) when the cost of general practitioner initiation and titration visits was added.

Cost of excess gastrointestinal events

Table 1 summarises the cost of gastrointestinal events. Significantly more admissions were associated with adverse events among patients randomly assigned to nicorandil (132 of 2561 for usual care, 194 of 2565 for nicorandil, $p < 0.05$ χ^2 test). The net number of extra bed days attributable to nicorandil was 367 for the general ward when all reported gastrointestinal events were considered. Four fewer intensive care bed days were used. The net cost in the group offered nicorandil was £83 522 (€123 045). The costs of general practitioner and clinic visits after discharge were £9646 (€14 211) higher in the group offered nicorandil. When only those gastrointestinal events considered by the investigator to be drug related were included, the net number of bed days fell to 123 for the general ward. One less intensive care bed day was used (net cost £28 443 (€41 903)).

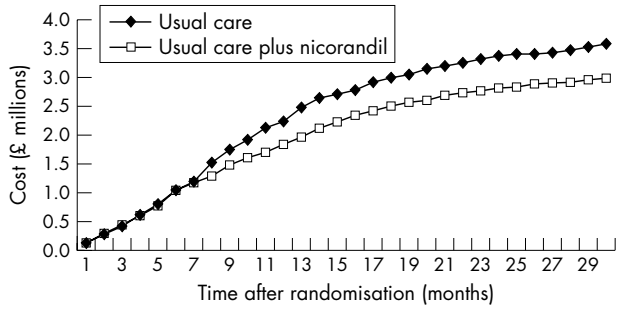

Figure 1 Cumulative cost of hospitalisation in each arm of the trial in months after randomisation.

Cost of cardiovascular and cerebrovascular admissions

Tables 2 and 3 summarise the number of patients admitted, the type of ward to which they were admitted, the number of days spent in hospital, the cause of admission, and the costs associated with these.

In the usual care arm, 27% of patients (683 of 2561) were hospitalised for a cardiovascular or cerebrovascular reason compared with 24% (609 of 2565) in the nicorandil arm ($p > 0.05$, χ^2 test, no significant difference). The number of admissions (including day cases) for cardiovascular or cerebrovascular reasons in each arm was 1132 for the usual

Table 3 Causes of hospital admissions and types of beds used

	Usual care	Usual care plus nicorandil	Nicorandil impact
Number of hospital admissions by cause			
Angina (without revascularisation)	251	179	−72
Cardiac catheterisation (angiography)	249	215	−34
Chest pain (without revascularisation)	157	149	−8
PTCA	116	98	−18
CABG	109	88	−21
AMI (without revascularisation)	66	51	−15
Heart failure or shock*	48	50	+2
Arrhythmia or conduction disorders*	28	36	+8
Non-transient stroke or CVA	24	24	0
Other cardiovascular cause of admission	80	74	−6
Type of hospital bed used			
Bed days in CCU/ICU	1098	893	−205
Bed days in other wards	5056	4337	−718

*No surgery or procedure.
AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CCU, coronary care unit; CVA, cerebrovascular accident; PTCA, percutaneous transluminal coronary angioplasty.

Table 4 Combined costs of drug, gastrointestinal events, and hospitalisations

	Primary analysis	Cost/patient	Secondary analysis	Cost/patient
Nicorandil	£596304	£232	£596304	£232
Net gastrointestinal adverse events	£28443	£11	£83522	£33
Net cost of cardiovascular admissions	−£625062	−£244	−£625062	−£244
CCU/ICU	−£186535	−£73	NA	NA
Other inpatient	−£428091	−£167	NA	NA
Day cases	−£10436	−£4	NA	NA
Net cost of care after discharge	NA	NA	−£20202	−£8
Net overall cost	−£315	−£0.12	£34562	£13

NA, not applicable.

care arm and 968 for the group offered nicorandil. Because the average length of stay in both treatment groups was identical, the reduction in admissions resulted in a reduction in the number of hospital bed days occupied by the nicorandil group. A reduction was seen in both CCU/ICU bed days and other types of bed use.

Admissions for cardiovascular procedures (for example, angioplasty and bypass surgery) were reduced, as well as those for events (for example MI, chest pain). Because these events are relatively infrequent, these differences did not achieve significance (χ^2 test).

The hospital costs in the group offered nicorandil were £625 062 (€920 848) lower than in the usual care arm. The mean cost for each patient was significantly lower in the nicorandil group (£1182 (€1746) *v* £1428 (€2104) in the usual care arm, p = 0.008, Wilcoxon two sample test). Figure 1 shows cumulative hospital costs over time for each group, plotted by taking account of the date of each episode compared with the date of entry to the trial.

The costs of general practitioner and clinic visits after discharge were £29 848 (€43 972) lower.

Combining costs and offsets

Table 4 shows the results of the primary analysis (which included costs of nicorandil, definite gastrointestinal events, and reduced hospitalisation). The overall net cost of care was slightly less in the nicorandil group because the cost of reduced hospitalisation outweighs the cost of the drug and possible gastrointestinal events. The net cost in the group offered nicorandil was −£315 (−€464) (or −£0.12 (−€0.18) for each patient).

Table 5 and fig 2 show the results of the secondary analysis (which included all gastrointestinal events and estimates of post-discharge care). The net cost in the nicorandil group was £34 562 (€50 947) (or £13 (€19) for each patient).

Incremental cost effectiveness ratios

In the primary analysis, the net cost for each IONA primary end point averted was −£5 (−€7) (table 5). This rose to £567 (€835) in the secondary analysis.

Taking definite acute coronary syndromes (fatal or non-fatal MI or unstable angina) as the benefit measure, the cost per event averted was −£8 (−€12) in the primary analysis, rising to £886 (€1305) in the secondary analysis.

Table 5 Incremental cost effectiveness ratios

	Primary analysis	Secondary analysis
Net cost/primary end point averted	−£5	£567
Net cost/acute coronary syndrome averted	−£8	£886
Net cost/event-free survivor	−£5	£516

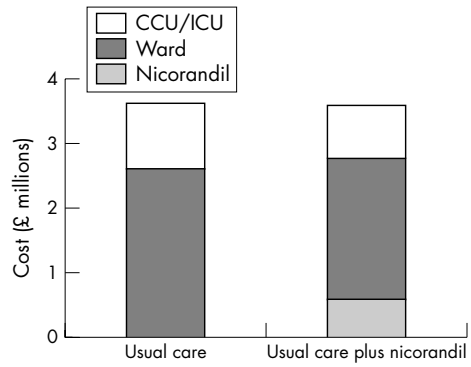

Figure 2 Components of total cost in each arm of the trial. CCU, coronary care unit; ICU, intensive care unit.

At the end of the trial 2069 patients in the usual care arm had not experienced a major cardiovascular event (CHD death, non-fatal MI, unstable angina, definite or probable angina, and stroke or hospital admission for transient ischaemic attack) and 2136 survivors in the group offered nicorandil were event-free. The net cost for each additional event-free survivor was −£5 (−€7) in the primary analysis and £516 (€760) in the secondary analysis.

Sensitivity analysis

The sensitivity analysis was based on the primary analysis above. Table 6 summarises the results. Increased stent use made little difference to the net cost because the number of angioplasties was not very different between the two groups (see table 3). Adjusting the costs of hospital stay, however, had more impact; the results were most sensitive to the cost of time spent on a cardiac surgery ward, then to the cost of ICU/CCU, and then to cost of cardiology bed days.

DISCUSSION

Angina pectoris places a huge economic burden on the health care systems of all developed countries.[6–9] This burden is rising relentlessly because of the increasing numbers of both elderly people (who are at most risk of CHD) and long term survivors with CHD in the aging populations of these societies.[10–12] The largest parts of the direct health care costs of angina are those due to hospital admissions and revascularisation procedures or operations.[4–9] It is therefore of great clinical and economic importance that new treatments for angina pectoris be cost effective or affordable.

The IONA trial evaluated the effect of nicorandil on the most clinically and economically important disease specific events experienced by patients with angina—that is, CHD death, non-fatal MI, or unplanned hospital admission with cardiac chest pain, with these events reflected in the primary end point of the study.[4–9] Coronary revascularisations were also accounted for.

Table 6 Sensitivity analysis

	Net cost of adding nicorandil	Net cost/ patient	Net cost/primary end point averted
Baseline values	−£315	−£0.012	−£5
Increase angioplasty costs by £100	−£2115	−£0.82	−£35
Increase angioplasty costs by £200	−£3915	−£2	−£64
Increase angioplasty costs by £500	−£9315	−£4	−£153
Reduce cardiology cost/day by 20%	£20878	£8	£342
Increase cardiology cost/day by 20%	−£21508	−£8	−£353
Reduce cardiac surgery cost/day by 20%	£64110	£25	£1051
Increase cardiac surgery cost/day by 20%	−£64741	−£25	−£1061
Reduce ICU/CCU cost by 20%	£36992	£14	£606
Increase ICU/CCU cost by 20%	−£37622	−£15	−£617

Nicorandil averts primary end point events at an average net cost of −£5 (−€7), due to the reduction in hospital admissions (and procedures) in the nicorandil group offsetting the cost of drug. This rises to £567 (€835) in the secondary analysis where the cost of the drug is no longer offset by the reduction in hospital admissions (and procedures) in the nicorandil group. The cost for each acute coronary syndrome averted is −£8 (−€12) in the primary analysis and £886 (€1305) in the analysis that considers all gastrointestinal admissions and outpatient costs. How does this incremental cost effectiveness ratio for nicorandil compare with other treatments? This is a difficult question to answer, as there are very few existing cost effectiveness analyses of antianginal drugs. Indeed, a recent and comprehensive systematic review could identify only one satisfactory analysis of this type (an American modelling study comparing the annual cost of three types of nitrates).[20 21] However, the range of cost effectiveness ratios for adjunctive nicorandil appears very attractive when compared with several other new treatments recently evaluated in a similar way.[22–24] In one clinical trial, the use of a platelet glycoprotein receptor IIb/IIIa antagonist in acute coronary syndromes resulted in an incremental cost effectiveness ratio of £9995 (€14 725) for each event avoided. The incremental costs of clopidogrel may be similarly high.[25] The cost per further revascularisation averted by the use of a coronary stent at the time of angioplasty (compared with angioplasty without a stent) has been calculated at £11 065 (€16 301). In a modelling analysis based on the second European stroke prevention study, the cost for each stroke averted of adding modified release dipyridamole to aspirin was £1900 (€2799) (at 1996 costs).[26] All of these figures are higher than the £886 (€1305) for each acute coronary syndrome averted even when all gastrointestinal admissions are included. As all of the above treatments have passed into common cardiological practice, we conclude that the cost effectiveness ratios of this order of magnitude must be broadly acceptable. We therefore argue that the use of nicorandil in line with the IONA protocol is also cost effective.

Though the present study has the strength of being based on real data, collected prospectively during a randomised clinical trial, it also has limitations. Firstly, patients enrolled into trials are not perfectly representative of general patient populations, so some allowances should be made in transferring results to day to day practice. Secondly, IONA specifically targeted high risk angina patients. Most treatments are more cost effective in higher risk patients, because the absolute risk reduction in events (leading to hospitalisations or procedures) is greater. The favourable cost effectiveness of nicorandil in these patients may not be generalisable to all patients with angina. A third limitation, shared by all analyses based on clinical trial, relates to the finite duration of follow up. However, attempting to model outcomes and costs beyond the end of trials is also problematic.[27]

In summary, the clinical benefits of nicorandil in high risk angina patients are reflected in favourable cost effectiveness ratios. Nicorandil, added to usual treatment, reduces the risk of important clinical events at a modest extra cost.

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Authors' affiliations

A Walker, A D McMahon, N J K Henderson, I Ford, Robertson Centre for Biostatistics, University of Glasgow, Glasgow, Scotland
J McMurray, H Dargie, S Hillis, Department of Cardiology, Western Infirmary, Glasgow, Scotland
S Stewart, Division of Health Sciences, University of South Australia, Adelaide, Australia
W Berger, Health Economics Division, Merck KGaA, Darmstadt, Germany
K Fox, Department of Cardiology, Royal Brompton Hospital, London, UK

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IMAGES IN CARDIOLOGY

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Congenital foramen of the left pericardium masquerading as left ventricular aneurysm

A 69 year old woman was referred for coronary artery bypass surgery following coronary angiography which revealed triple vessel disease. Left ventriculogram was reported as ''left ventricular aneurysm'' (panel A). However, on close observation of the cine ventriculogram, the ''aneurysm'' could be seen to contract during systole.

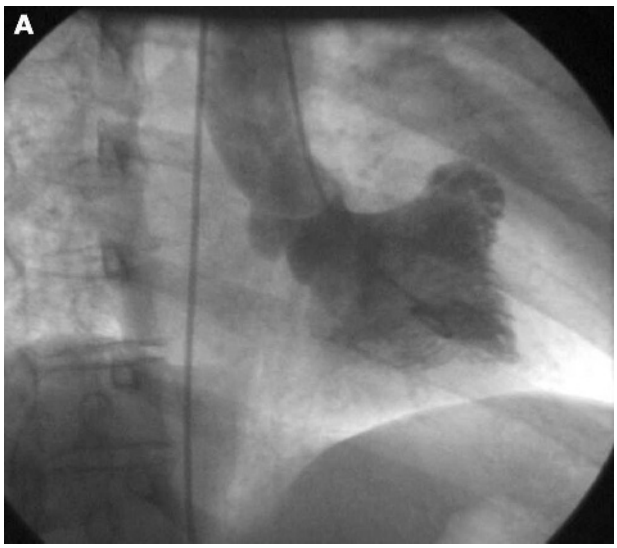
A revised diagnosis of congenital foramen of the left pericardium was made. This was confirmed at the time of surgery (panel B). The left atrial appendage and part of the lateral wall of the left ventricle was herniating through the defect.

The latter was extended in the cephalad direction to accommodate the left internal mammary artery pedicle used to bypass the left anterior descending coronary artery.

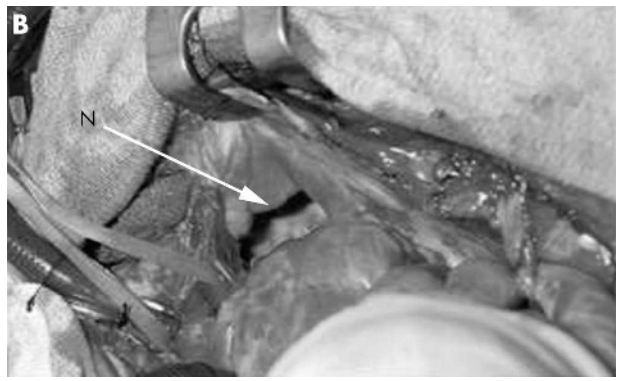
Congenital foramen of the left pericardium is rare. To date less than 50 cases have been described in the literature. It is believed that the defect is caused by a tear in rather than a failure of the pleuro-pericardial membrane to close. Common presentations include angina, dyspnoea, myocardial infarction, syncope, and occasionally death. A third of patients are asymptomatic. The defect is sometimes visible on plain chest radiograph. ECG may reveal ST segment abnormalities suggestive of coronary insufficiency caused by impingement of the rim of the defect on the coronary tree.

The diagnosis is confirmed by echocardiography or during left ventricular cinegram. Magnetic resonance imaging and thoracoscopy have also been employed to confirm the diagnosis. The management is directed to prevent incarceration of the myocardium. The defect can either be closed or enlarged surgically as described above.

T BinEsmael
H Luckraz
A Azzu
heymanluckraz@aol.com



Left ventricle cinegram showing the herniated left ventricular wall through the pericardial defect.



Intraoperative photograph showing the small congenital foramen of the left pericardium. N, neck of pericardial hernia.